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B. Webb
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

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In re US Patent Application of
Thomas W. Astle
Serial No. 09/460,107
Filed: December 13, 1999
Title: CONTINUOUS POLYMERASE CHAIN REACTION PROCESS WITH MULTIPLE TEMPERATURE STATIONS

Date: March 5, 2001.

Assistant Commissioner for Patents
Washington DC 20231

BRIEF OF APPELLANT

This is an appeal from the final rejection of the Examiner, dated October 3, 2000 (Paper No. 5), rejecting Claims 12-28.

REAL PARTY IN INTEREST [37 CFR 1.192(c)(1)]

The real party in interest is the party named in the caption.

RELATED APPEALS AND INTERFERENCES [37 CFR 1.192(c)(2)]

There are no related appeals or interferences.

STATUS OF CLAIMS [37 CFR 1.92(c)(3)]

The status of the claims set out in Paper No. 5 was and is:

Claims pending: 12-28.

Claims withdrawn from consideration: none.

Claims allowed: none.

Claims objected to: none.

Claims rejected: 12-28.

SUMMARY OF THE INVENTION [37 CFR 1.192(c)(5)]

Applicant's invention is directed to an apparatus for performing a reagent protocol using polymerase chain reaction (PCR), but does not claim a method for performing a specific PCR protocol. Accordingly, a more accurate titled for a patent application containing the present claims would be more CONTINUOUS POLYMERASE CHAIN REACTION APPARATUS WITH MULTIPLE TEMPERATURE STATIONS and an amendment proposing that title will be submitted if there are further proceedings in the application.

Principal objects of the claimed invention are to provide an apparatus for PCR processing that greatly reduces temperature transient times, that is continuous, and that can be used economically for both small and large numbers of DNA samples.

The apparatus is used with a multi-well carrier tape (20, Figure 1) having pluralities of wells (32) and sprocket holes (70), the latter being provided to assist in indexing the carrier tape using an indexing mechanism (120, Figure 2) so as to provide a positive position controlled drive system. The apparatus includes a multi-well pipettor head (140). A second transfer station (140, Figures 2 and 3) is identical to the first transfer station. The transfer stations are used to add reagents and DNA to the wells. Following the transfer stations is a heat sealing station (216, Figures 2 and 3) that covers the wells with a heat seal material (212, Figure 2).

Following heat sealing, the carrier tape moves through a series of heat transfer stations (240, Figures 2 and 3). Following that, the heat sealing materials is stripped from the carrier tape (Figure 6) and the contents of the wells can be accessed for further processing. Various indicia readers (132, 182, and 400, Figure 1) are used for identifying the individual sections of carrier tape.

Mechanical details of the heat transfer stations may be understood from inspection of Figures 4 and 5 and the accompanying text.

ISSUES [37 CFR 1.192(c)(6)]

Since the grounds of rejection and the arguments against rejection are closely related, the grounds of rejection and the arguments are taken together.

The Examiner has rejected claims 12-28 under 35 USC 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to make and/or use the invention. Claims 12-28 have been rejected under 35 USC 112, first paragraph, as containing subject matter which was not described in the Specification in such a way as to reasonably convey to one skilled in the art that the inventor, at the time the application was filed, had possession of the claimed invention. Claims 12-28 have been rejected under 35 USC 112, second paragraph, as being indefinite. Claims 12-28 have been rejected under 35 USC 112, second paragraph, as being vague and indefinite. Claims 12-28 have been rejected under 35 USC 112, second paragraph, as being incomplete.

GROUPING OF CLAIMS [37 CFR 1.192(c)(7)]

To the extent that arguments are presented below with respect to specific claims, it is Applicant's intention that those claims shall not stand or fall with the claims with which they are grouped.

ARGUMENT [37 CFR 1.192(c)(8)]

It is noted, first, that the same descriptive content was used in a $ 1,000,000.00 SBIR Grant that was filed with NIH. There haven't been any similar questions resulting from that filing.

All the ground of rejection seem to stem from the Examiner's understanding that the present invention is intended to teach PCR processing. On the contrary, it is not the intention of the disclosure to teach PCR processing, since that is well covered elsewhere. It is the intention of the invention to provide an apparatus that can be used to perform PCR processing.

The Examiner indicates *"The specification does not enable the making of the apparatus for performing a reagent protocol using polymerase chain reaction with undefined size of reagent wells"*. It is assumed by this that he is referring to the description portion of the application (pages 9 through 21). The patent application describes an apparatus and method of using that apparatus for performing PCR. The actual P[illegible] protocol is a function of the individual using the apparatus. The application [illegible] not trying to teach PCR protocols. They are well defined in the industry and [illegible] odified as necessary by the researcher using the apparatus. The apparatus is a r[illegible]el design to meet the generic requirements of PCR protocols.

In the basic sense, the P[illegible]R protocol requires the addition of prescribed reagents such as DNA, forwarc[illegible]nd reverse primers, and master mix, in set amounts. These reagents are t[illegible]ı temperature cycled through denaturing, annealing, and extension tempe[illegible]tures to achieve the amplification desired for the protocol. This process is w[illegible]l detailed in the academic literature. True, there may be some experimenting wi[illegible] the parameters of the PCR protocol to achieve the desired end result. That hc[illegible]ever does not mean experimentation with the apparatus of the invention. Th[illegible]ıpparatus of the invention provides the means to

the practitioner to change and control the parameters for the specific protocol being developed.

The Examiner also makes an issue of the undefined size of reagent wells. The size and spacing of the reagent wells is also a function of the specific protocol for which the apparatus of the present invention is being used. In the Biotechnology field of work, the *de facto* standard is the microplate. As is well known in the art, this can be, for example, in the 96-, 384-, or 1536-well format. The 96-well format is an 8 x 12 matrix on 9mm centers. The brim volume of the well is 300μL to 350μL. The 384-well format is a 16 x 24 matrix on 4.5mm centers. The brim volume is 80μL to 100μL. The 1536 format is 32 x 48 on 2.25mm centers. The brim well volume is 10μL.

Today, virtually all high volume, PCR work is accomplished in the 96- or the 384-well format. The carrier tape described in the present application can also be provided in various formats, depending on the application requirements. For that reason, the claims of the application do not cover the well pattern. However, the description does describe a pattern of a 16 x 24 array on 4.5mm centers with a well volume of 10μL (page 9 and Fig. 1).

It is not clear why the Examiner feels the reagent wells are undefined. The description gives a specific example, but other patterns could be used depending upon the specific application.

The Examiner makes an issue that *"The specification does not set forth any software by which such an apparatus is to be operational, ... "* The reason for this is that the use of software is only one way to operate the line. By no means is it a requirement. The Specification details the functions of each station and how they fit into the workflow diagram.

As a case in point, consider the main drive methods. By definition, this must be an indexing drive that moves the carrier tape from one processing

station to the next. This is common production line technology. This indexing drive can be a purely mechanical motion. It can be derived by commercial components, such as Geneva motions or walking beam motions. The entire system could be controlled with straight, forward relay logic. However, today a PLC (Programmed Logic Controller) would be used.

There is no doubt a software system could be used. Stepper motors or servomotors could be used for the indexing motion. However, this again is simply an option that is open to any individual designing the line based on the novel concepts of a sprocket driven carrier tape disclosed in this patent application. The drawing figures plus the description, describe the sequence and functions required.

The unique and novel concept this patent application teaches is that of a sprocket driven carrier tape with self contained reagent wells, that are automatically indexed between processing stations to achieve a defined purpose, such as a PCR reaction or other biological assays. The methods of process control are many and well established to anyone who would practice the art.

In the prototype system that is being built according to the invention, the indexing will be a walking beam type of drive, using air cylinders controlled by solenoid valves. There will be a simple logic sequence controlling the solenoid valve. This is a low cost, simple drive system. On a larger production line, a mechanical cam driven walking beam could be used to drive to achieve the desired motion.

The Examiner makes the statement *"Note that the specification does not provide adequate guidance to teach how to perform the polymerase chain reaction such as how to loading and unloading of the machine and how to set up a program of a polymerase chain reaction."* It is not the intent of this patent to teach PCR. That is well covered, for example, in the basic patents issued to

Kary Mullis, ET. (US Patent Nos. 4,683,195; 4,683,202; 4,965,188; and 5,075,216). The information is also contained in many academic textbooks. The intent of this patent application is to describe a novel and unique apparatus and method of using the apparatus to perform PCR type protocols.

The multiple well pipettors described in this application are in common use within the field of art. They are described in detail in US Patents Nos. 5,736,105 and 5,598,343 and are well known by those having ordinary skill in the art. Therefore, the details of their operation are not reiterated in the present application. As for loading and unloading the machine, it's not clear what additional information the Examiner is requesting. From the description, it is obvious that an empty roll of carrier tape is placed on the unwind stand. Reagents are added to the wells in the carrier tape by the multiple well pipettors. These devices are in common use in PCR and other biological protocols. They would be set up to add the specific reagents called for by the desired protocol.

The Examiner indicates the following *"Note that these undue experimentations will include but not limit to: (1) redesign a reagent well with a size which fit the protocol of polymerase chain reaction: (2) set forth a software by which such an apparatus is to be operational: (3) how to loading and unloading of the machine and how to set up a program of a polymerase chain reaction. These undue experimentations would require several years to complete."*

In regard to (1) above, the practitioner does not need to redesign a reagent well. The protocol volumes are simply matched to the well size available. Many PCR reactions are run in 96-well format, others in 384-well format. Marshfield Clinic operates the NIH Genotyping Facility for NIH. They do 6 million genotypes a year. They are currently done at the 1μL to 2μL levels in a 96 well format. That could just as easily be done on the apparatus proposed

by this application at a saving in time and labor and with a much greater throughput. They are currently waiting for the completion of the prototype system.

In regard to (2) above, the point the Examiner makes on software was addressed before. Complex software is neither required nor desired. Like all automated systems, this apparatus will have a logic control system. To be of use, it must be easily understood by the end user. The logic system that is used could be one of many. It is fully covered by existing art. It would not be novel and unique and this is not part of this invention.

In regard to point (3), it is assumed the Examiner means loading the various reagents and supplies on the line. Since the protocols remain the same, there is no learning curve involved. The only difference is that the same devices are being used in a unique and novel manner to provide a higher level of throughput with a reduction in the cost of reagents and consumables.

Presence or Absence of Working Examples

The inventor has three (3) years of work and development into the present invention. Specific working examples of the specific elements are the basis of the descriptive write-up.

The State of The Prior Art

It is agreed that the apparatus described by this invention is a novel and undeveloped area of the art. That is why this application was filed.

Relative Skill of Those in the Art

Again, the Examiner seems to believe that the present application is teaching PCR. That is covered by other patents. It is agreed that someone using PCR has a purpose in mind, and that individual needs to be skilled in the use and functions of PCR in various areas of scientific discovery. However, the individual using an automated processing line, to process in excess of 6 million

genotypes annually, does not require a Ph.D degree. He or she is simply a technician trained to operate a specific piece of apparatus.

The Predictability or Unpredictability of the Art

Again, the Examiner is confusing the operation of a novel mechanical processing line with the uncertainty of scientific discovery in the areas of unknown science.

The Breadth of the Claims

It is respectfully submitted that the Examiner is very narrow sighted in the assumption that everything must be computer controlled. In practice, the opposite is desired. Reliability and simplicity go hand in hand. A temperature controlled thermocycling system is well defined. As before, in simplest terms, this can be accomplished with relay logic. The cost and complexity of a computer controlled system is not cost justified.

The Examiner seems to feel that a complex computer controlled system is required. That is not the case. The description of operation provided details the logic of the systems operation. That is the part that is unique and novel, which is the basis for this application. How the logic is executed is the option of the system designer. To any one involved in the art, not even skilled, there are a number of options; relay logic, hardwired logic circuits, PLC (Programmed Logic Controller), or a simple I/O map on a computer controlled system. These are not novel and this application does not propose to select one over the other.

A detailed sequence of operation is covered in the Specification. A schematic flow diagram is presented along with a detailed description of the operation of each section and its importance to the overall operation.

It pointed out that the processing line is continuous. Whatever means are chosen by the designer to index the carrier tape, it will not only move the carrier tape through the reagent addition steps but concurrently through the temperature

cycling steps inherent in a PCR reaction. The term "means" is used as a generic term to cover any of the many indexing methods that may be used.

The term "thermoplastic" and its use in these claims is hardly indefinite. Thermoplastic web refers to those plastic materials that can be formed with heat and when the heat is removed will remain dimensionally stable. There is a wide variety of well known thermoplastic materials from which the carrier tape can be formed depending on the application. For chemical resistance, polypropylene would be used. For applications requiring clarity, polycarbonate may be the choice. Polyester resins offer another choice. These choices and the logic for their use are detailed on page 10 of the specification.

The term "single and multiple well pipettor" is well known to anyone in this field. The details are further taught by US Patents Nos. 5,736,105 and 5,598,343. They are common units that are in commercial use from several sources.

The term "specific time controlled period" is not defined by this invention. This invention provides the mean to control the specific times required by the protocol using this invention. It is respectfully submitted that the Examiner is again mixing the apparatus with the use for which the apparatus is designed.

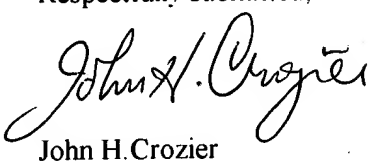
The omission of a "computer temperature controlled system" is only in the Examiners' view of how he would control the system. It is not an omission on the part of this application.

It is further noted that the Hansen et al. patent cited by the Examiner appears to have about the same degree of disclosure as the present application.

In view of the above, it is respectfully submitted that the Examiner's rejection is in error and should be reversed.

Date: March 5, 2001.

Respectfully submitted,



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12. An apparatus for performing a reagent protocol using polymerase chain reaction, comprising:

(a) means to index patterns of reagent wells on a continuous basis through at least one step of reagent addition to said reagent wells; and

(b) means to index said patterns of reagent wells on a continuous basis through a plurality of individual heat transfer stations, whereby at each of said individual heat transfer stations, said patterns of reagent wells are subjected to a unique temperature change to cause one amplification step, with said plurality of individual heat transfer stations providing total amplification required for said protocol.

13. An apparatus, as defined in Claim 12, further comprising: means to seal said reagent wells following said at least one step of reagent addition to said wells.

14. An apparatus, as defined in Claim 12 wherein: said reagent wells are disposed in patterns of said reagent wells in a thin thermoplastic web.

15. An apparatus, as defined in Claim 14, wherein: said reagent wells are formed in said thermoplastic web by embossing.

16. An apparatus, as defined in Claim 14, wherein: said reagent wells are formed in said thermoplastic web by thermoforming.

17. An apparatus, as defined in Claim 14, further comprising: a plurality of precision located indexing holes defined through an edge of said thermoplastic web to accommodate a tractor type of position controlled indexing drive.

18. An apparatus, as defined in Claim 17, wherein: said tractor type of position controlled indexing drive is selected from the group consisting of: walking beams, cam drives, geneva motions, electronic stepper drives, and pneumatic indexing mechanisms.

19. An apparatus, as defined in Claim 12, further comprising: a variable code of holes defined through said thermoplastic web to provide positive identification of each said patterns of reagent wells.

20. An apparatus, as defined in Claim 19, further comprising: means to sense said holes, said means to sense said holes being selected from the group consisting of: physical contact, pneumatic sensing, and photometric sensing.

21. An apparatus, as defined in Claim 12, further comprising: at least one single or multiple well pipettor to accomplish said at least one step of reagent addition.

22. An apparatus, as defined in Claim 21, further comprising: said at least one single or multiple well pipettor is adapted to transfer reagents from reservoirs of single or multiple reagents to said reagent wells.

23. An apparatus, as defined in Claim 22, wherein: said reservoirs of regents are refillable or exchanged automatically from stacks to provide continuous operation.

24. An apparatus, as defined in Claim 13, wherein: said patterns of reagent wells can be sealed to provide a liquid tight but peelable seal as provided by pressure sensitive adhesive or heat seal methods.

25. An apparatus, as defined in Claim 13, wherein: separate heat exchanger compartments can be clamped to a lower surface of said thermoplastic web to form a liquid tight seal around individual said patterns of reagent wells.

26. An apparatus, as defined in Claim 25, further comprising: means to cause heat exchange fluid to flow through each of said separate heat exchanger compartments for specific time controlled periods.

27. An apparatus, as defined in Claim 13, further comprising: means to peel sealing material from a top of said thermoplastic web to provide access to said reagents by a single or multiple well pipettor.

28. An apparatus, as defined in Claim 27, further comprising: a heated pressure roller in contact with said sealing material to apply a line of heat across said thermoplastic web to soften bonding of said sealing material to said thermoplastic web to permit ease of removal by applying tension to said sealing material.